ATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 March 2000 (17.03.00)	
International application No. PCT/IB99/01424	**Applicant's or agent's file reference** BLOcb226/79
International filing date (day/month/year) 16 July 1999 (16.07.99)	**Priority date** (day/month/year) 16 July 1998 (16.07.98)
Applicant THEZE, Jacques et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   02 February 2000 (02.02.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

15

PATENT COOPERATION TREATY

REC'D 11 SEP 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BLOcp226/79P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/01424	16/07/1999	16/07/1998
International Patent Classification (IPC) or national classification and IPC C07K16/24		
Applicant INSTITUT PASTEUR et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2000	05.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weijland, A Telephone No. +49 89 2399 7490

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01424

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-32 as originally filed

Claims, No.:

1-25 as originally filed

Drawings, sheets:

1/16-16/16 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 7, 11, 12, 14, 15, 18-25
	No:	Claims	1-5, 8-10, 13, 16, 17
Inventive step (IS)	Yes:	Claims	6, 7
	No:	Claims	1-5, 8-25
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: ECKENBERG R ET AL., : 'Analysis of human IL-2/IL-2 receptor beta chain interactions: Monoclonal antibody H2-8 and new IL-2 mutants define the critical role of alpha helix-A of IL-2.' CYTOKINE , vol. 9 (7), 1997, page 488- 498
D2: WO 91 02000 A (SERAGEN INC) 21 February 1991 (1991-02-21)
D3: WO 90 00565 A (AMGEN INC) 25 January 1990 (1990-01-25)
D4: MOREAU J-L ET AL., : 'Characterization of a monoclonal antibody directed against the NH2 terminal area of interleukin-2 (IL-2) and inhibiting specifically the binding of IL-2 to IL-2 receptor beta chain (IL-2R-beta)' MOLECULAR IMMUNOLOGY, vol. 32 (14-15), 1995, page 1047-1056

SECTION V

1. Novelty (Article 33(2) PCT)

1.1 The subject matter of claims 1-5, 8-10, 13, 16, 17 is not novel.

Claims 1 and 16, relating to an antibody which binds to a peptide consisting of sequence SEQ ID NO.:2 or 4 and a peptide consisting of the sequence SEQ ID NO.:2 or 4 respectively, are anticipated by D1. The same applies to claims 2, 4 and 17. D1 (abstract; page 489, left column, fifth paragraph) describes an anti human IL-2 mAB (H2-8), produced after immunization with peptide having amino acids 1-30 (SEQ ID NO.: 4, claims 1, 2, 4,16,17) of IL-2, which recognizes the region occupied by Asp20. mAB H2-8 specifically inhibits the IL-2 proliferation of TS1[SPEC0803]. The peptide 1-30 of IL-2 was able to inhibit the binding of mAB H2-8 to IL-2, this peptide adopts a structural conformation close to native IL-2.

Claims 9, 13 and 16, relating to the use of a peptide comprising sequences SEQ ID NO's: 2 or 4 (claims 9, 13) and the peptide having the sequence SEQ ID NO.:2 or 4 (claim 16), are anticipated by D2 and D3. The same applies to claim 17. D2 (page 1, second paragraph) describes the IL-2/diphtheria toxin hybrid (peptide **having** sequence SEQ ID NO.:2 or 4, claim 16, claim 17) shown to inhibit the rejection of transplanted organs and to be a potential therapeutic agent (claims 9 and 13) in the treatment of certain cancers and autoimmune diseases in which IL-

2R plays a role. D3 (page 1, fourth paragraph; page 7, second paragraph) describes that IL-2 (claims 16 and 17) has application in the treatment of neoplastic and immunodeficiency diseases. Pharmaceutical compositions for Il-2 therapy comprising IL-2 and suitable diluents or adjuvants are described (claims 9 and 13).

Claims 1 and 16 are anticipated by D4. The same applies to claims 2, 3 and 17. D4 (abstract; page 1051, left column, paragraph 8) describes mAB 19B11/B and polyclonal antibodies (claims 1-3) recognizing peptide 1-30 (claims 16 and 17) of IL-2 with high affinity.

Claims 5 and 10, relating to a DNA sequence encoding a peptide consisting of sequence SEQ ID NO.:2 or 4 (claim 5) or a vector containing this DNA sequence, are implicitly anticipated by the peptide 1-30 of IL-2 in D1, since this peptide is the translational product after expression of these DNA sequences.

Claim 8, related to a method of inhibiting the activity of an IL-2R, is anticipated by D1. D1 (Figure 5; page 491, left column) describes a method to inhibit the proliferation of the TS1β cell line. Different concentrations of mAB H2-8 were used to reduce the IL-2 proliferation of TS1-β.

1.2 The subject matter of claims 6-7, 11-12, 14, 15, 18-25 is novel.

The subject matter of claims 6-7,11 is not disclosed in the prior art documents. The same applies to claims 12; 14; 15; 18-25.

2. Inventive Step (Article 33(3) PCT).

2.1 The subject matter of claim 11 does not appear to involve an inventive step.

D2 is considered to be the closest prior art. D2 (page 1, second paragraph) describes the use of the IL-2/diphtheria toxin hybrid as potential therapeutic agent in the treatment of certain cancers and autoimmune diseases in which IL-2R plays a role. Claim 11 differs from D2 in that claim 11 describes the use of a vector

containing SEQ ID No's 2 or 4 for the preparation of a medicament useful to induce in a patient selected useful activities of IL-2.

The technical problem to be solved would appear to reside in finding an alternative molecule useful to induce in a patient IL-2 activity.

The skilled person, equipped with the knowledge of D2, would be motivated to turn to D1 for the solution of this particular problem. This document is concerned with a similar problem, that is the search for functional homologs of IL-2. It is there suggested to solve the problem by using a mutant peptide comprising the 1-30 amino acids of IL-2. This suggestion essentially corresponds to the feature which distinguish claim 11 from the prior art, since the vector mentioned in claim 11 expresses SEQ ID NO.:4. The skilled person would know how to derive the DNA sequence from the peptide encoding amino acids 1-30 of IL-2 for use in the vector of claim 11.

2.2 The subject matter of claim 18-25 does not appear to involve an inventive step.

Dependent claims 18-25 do not contain any features which, in combination with the features of claim 16 to which they refer, meet the requirements of the PCT in respect of inventive step, since the substitution of the peptide sequence of IP130 with the conservative amino acids form merely obvious alternatives for the skilled person without resulting in any special effect whatsoever.

2.3 The subject matter of claim 12, 14 and 15 does not appear to involve an inventive step.

Dependent claims 12, 14 and 15 do not contain any features which, in combination with the features of claim 9 to which they refer, meet the requirements of the PCT in respect of inventive step, since the use of peptides in admixtures comprising a cytokine to increase the activity without resulting in any special effect whatsoever are merely obvious alternatives for the skilled person.

2.4 The subject matter of claim 6-7 would appear to involve an inventive step. D1 is considered to be the closest prior art. D1 (page 489, left column, fifth

paragraph) describes that the peptide having the amino acids 1-30 of IL-2 was able to inhibit the binding of mAB H2-8 to IL-2 and that this peptide adopts a conformation close to native IL-2. Claims 6-7 differ from D1 in that said claims describe:

- a method of detecting in vitro the presence of activity of IL-2R comprising incubation with the 1-30 IL-2 peptide (claim 6).

- methods for inhibiting the activity of an IL-2R by using the 1-30 IL-2 peptide (claim 7) as inhibitor.

These methods are not suggested in the prior art, since it was not shown in the prior art documents that the 1-30 IL-2 peptide can bind to IL-2R, despite that the peptide can inhibit the binding of mAb H2-8 to IL-2.

SECTION VII

3. The term "bind" in claim 8 needs to read probably "binding".

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 is not mentioned in the description, nor are these documents identified therein.

5. The application should be self contained (see further Guidelines C-II 4.17) and phrases "and incorporated by reference..." as mentioned on page 19 (line 12) contravene this requirement.

6. The references made to the Figure 8(A) (page 5, line 15), Figure 8(B) (page 5, line 17), and 8(C) (page 5, line 22) are not clear.

SECTION VIII

7. Claim 4 is not clear (Article 6 PCT). In said claim a hybridoma is identified by way of a trivial designation, which is meaningless to a person skilled in the art.

In order to meet the requirements of Article 5 and Rule 13bis PCT, copies of the deposition receipts or an equivalent proof needs to be present (see the Guidelines C-II 6.3).

8. The vague and imprecise statement in the description on page 32 (second paragraph) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, PCT/GL/3 III, 4.3a).

9. The applicant attributes to the term "R groups" in claims 18-20 a special meaning (see also page 12, line 32 of the description), which was not generally known in the technical field concerned at the relevant filing date and contravenes thereby the requirements of Article 6 PCT.

10. Claims 9 and 13 suffer from lack of clarity (Article 6 PCT), because they are formulated as second medical indication claims, but are not defined by a medical indication. The passage "..useful to induce in a patient selected useful activities.." in claim 9 or "..in an amount able to induce said useful activities" in claim 13, define an effect to be obtained, rather than a medical indication (i.e. a disease).

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 99/01424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/24 C07K14/55 C12N15/26 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ECKENBERG R ET AL., : "Analysis of human IL-2/IL-2 receptor beta chain interactions: Monoclonal antibody H2-8 and new IL-2 mutants define the critical role of alpha helix-A of IL-2." CYTOKINE , vol. 9 (7), 1997, page 488-498 XP000856633 cited in the application the whole document --- -/--	1-4,6-8, 16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1999	14/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

A D

ATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
BL0cb226/79		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 99/01424	16/07/1999	16/07/1998
Applicant		
INSTITUT PASTEUR et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readible form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PEPTIDES OF IL-2 AND DERIVATIVES THEREOF AND THEIR USE AS THERAPEUTIC AGENTS

5. With regard to the **abstract**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Compositions having IL-2-like activity and their use in the treatment or prevention of undesirable immune reactions such as graft rejection or autoimmune disorders, for example, rheumatoid arthritis. These compositions are defined as : a) peptides from N-terminus from IL-2 inhibiting or mimicking the binding of helix A of IL-2 to a subunit of a IL-2R, inducing phosphorylation of the subunit of the IL-2R; or b) antibodies which recognize the peptide of the invention, and the therapeutic use of these antibodies.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/24 C07K14/55 C12N15/26 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ECKENBERG R ET AL., : "Analysis of human IL-2/IL-2 receptor beta chain interactions: Monoclonal antibody H2-8 and new IL-2 mutants define the critical role of alpha helix-A of IL-2." CYTOKINE , vol. 9 (7), 1997, page 488-498 XP000856633 cited in the application the whole document --- -/—	1-4,6-8, 16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1999	14/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/IB 99/01424

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU J-L ET AL., : "Characterization of a monoclonal antibody directed against the NH2 terminal area of interleukin-2 (IL-2) and inhibiting specifically the binding of IL-2 to IL-2 receptor beta chain (IL-2R-beta)" MOLECULAR IMMUNOLOGY, vol. 32 (14-15), 1995, page 1047-1056 XP000856750 cited in the application the whole document	1-8
A	XU D ET AL., : "Biological and receptor-binding activities of human interleukin-2 mutated at residues 20Asp, 125Cys or 127Ser." EUROPEAN CYTOKINE NETWORK , vol. 6 (4), 1995, page 237-244 XP000856616 the whole document	6-8, 16-24
X	WO 91 02000 A (SERAGEN INC) 21 February 1991 (1991-02-21) page 9 abstract	9,13,16
X	WO 90 00565 A (AMGEN INC) 25 January 1990 (1990-01-25) page 25 page 4, line 1 -page 5, line 20	9,13,16

1

INTERNATIONAL SEARCH REPORT

ıation on patent family members

ɪrnational Application No
PCT/IB 99/01424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9102000 A	21-02-1991	AU 6179990 A	11-03-1991
		CA 2064696 A	03-02-1991
		EP 0485497 A	20-05-1992
		JP 4507250 T	17-12-1992
		NZ 234674 A	25-02-1992
WO 9000565 A	25-01-1990	AU 627477 B	27-08-1992
		AU 3877689 A	05-02-1990
		EP 0378666 A	25-07-1990
		JP 3500415 T	31-01-1991

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07K 16/24, 14/55, C12N 15/26, G01N 33/53 — A1

(11) International Publication Number: **WO 00/04048**

(43) International Publication Date: 27 January 2000 (27.01.00)

(21) International Application Number: PCT/IB99/01424

(22) International Filing Date: 16 July 1999 (16.07.99)

(30) Priority Data:
09/116,594 16 July 1998 (16.07.98) US

(71) Applicant *(for all designated States except US)*: INSTITUT PASTEUR [FR/FR]; 25–28, rue du Docteur Roux, F–75724 Paris Cedex 15 (FR).

(72) Inventors; and

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(74) Agents: ORES, Béatrice et al.; Cabinet Orès, 6, avenue de Messine, F–75008 Paris (FR).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PEPTIDES OF IL–2 AND DERIVATIVES THEREOF AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

Compositions having IL–2–like activity and their use in the treatment or prevention of undesirable immune reactions such as graft rejection or autoimmune disorders, for example, rheumatoid arthritis. These compositions are defined as: a) peptides from N–terminus from IL–2 inhibiting or mimicking the binding of helix A of IL–2 to a subunit of an IL–2R, inducing phosphorylation of the submit of the IL–2R; or b) antibodies which recognize the peptide of the invention, and the therapeutic use of these antibodies.

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DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/24 C07K14/55 C12N15/26 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ECKENBERG R ET AL., : "Analysis of human IL-2/IL-2 receptor beta chain interactions: Monoclonal antibody H2-8 and new IL-2 mutants define the critical role of alpha helix-A of IL-2." CYTOKINE , vol. 9 (7), 1997, page 488-498 XP000856633 cited in the application the whole document --- -/--	1-4,6-8, 16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1999	14/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU J-L ET AL., : "Characterization of a monoclonal antibody directed against the NH2 terminal area of interleukin-2 (IL-2) and inhibiting specifically the binding of IL-2 to IL-2 receptor beta chain (IL-2R-beta)" MOLECULAR IMMUNOLOGY, vol. 32 (14-15), 1995, page 1047-1056 XP000856750 cited in the application the whole document	1-8
A	XU D ET AL., : "Biological and receptor-binding activities of human interleukin-2 mutated at residues 20Asp, 125Cys or 127Ser." EUROPEAN CYTOKINE NETWORK , vol. 6 (4), 1995, page 237-244 XP000856616 the whole document	6-8, 16-24
X	WO 91 02000 A (SERAGEN INC) 21 February 1991 (1991-02-21) page 9 abstract	9,13,16
X	WO 90 00565 A (AMGEN INC) 25 January 1990 (1990-01-25) page 25 page 4, line 1 -page 5, line 20	9,13,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/01424

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WO 9102000 A	21-02-1991	AU 6179990 A	11-03-1991
		CA 2064696 A	03-02-1991
		EP 0485497 A	20-05-1992
		JP 4507250 T	17-12-1992
		NZ 234674 A	25-02-1992
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		AU 3877689 A	05-02-1990
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